NUOVE TERAPIE NEI LINFOMI B AGGRESSIVI E NEL MIELOMA MULTIPLO

Algoritmo terapeutico nel paziente FIT

Renato Zambello, MD

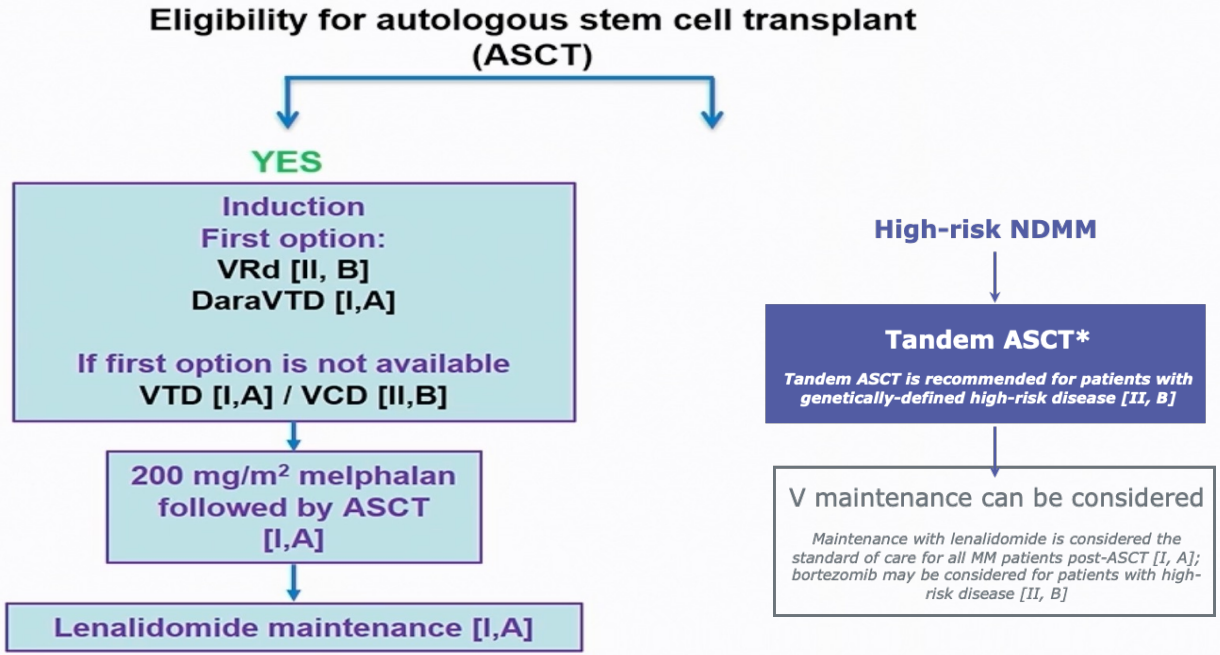
CRO Aviano (PN) - 9 ottobre 2024

Convegno Regionale SIE

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Menarini Stemline Italia S.r.l.						X	
Amgen						X	
Sanofi						X	
GSK						X	
Oncopeptides						X	
Janssen Cilag						X	

Convegno Regionale SIE

Front-line treatment of TE-NDMM outside clinical trials (EHA-ESMO guidelines 2021)

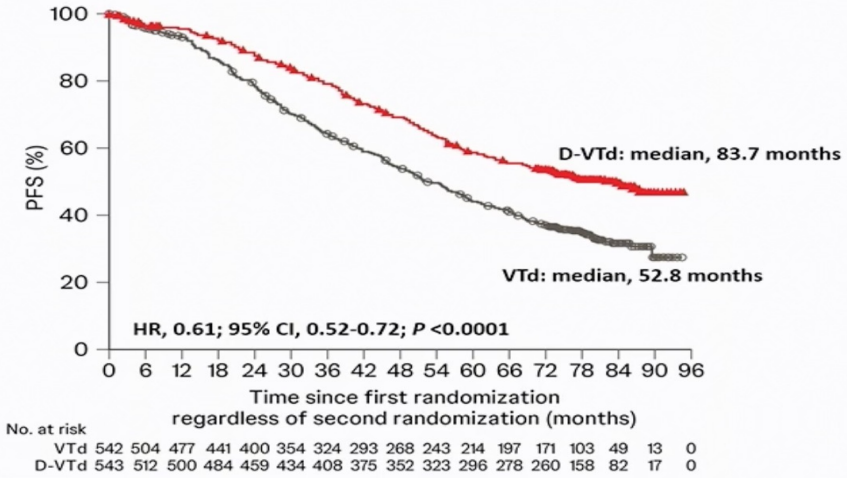


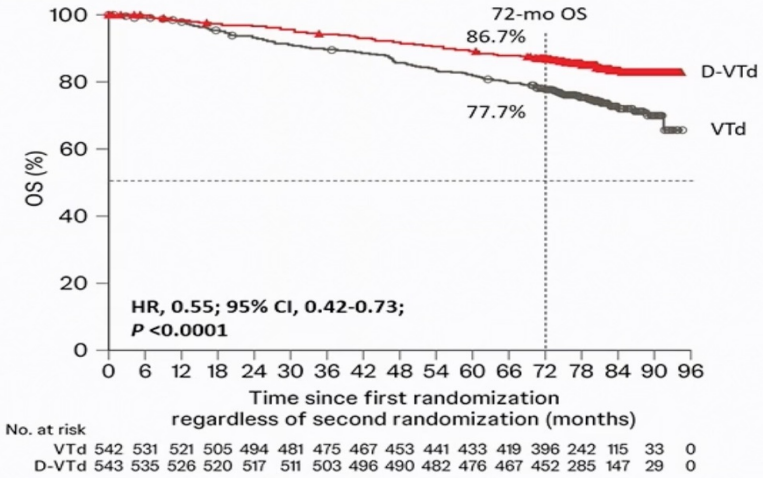
Dimopoulos MA et al. HemaSphere 2021, 5:2(e528)
Slide courtesy of Prof. Moreau

Dara-VTD Followed by Dara Maintenance in ND TE Myeloma patients (CASSIOPEIA): >6 Year Update

D-VTD vs VTD (post-conso) ≥CR 39% vs 26% *(p=0.001)*
MRD (10^{-5}) neg in CR: D-VTD 34% vs 20% *(p<0.0001)*

Progression-free survival and overall survival from first randomization regardless of second randomization

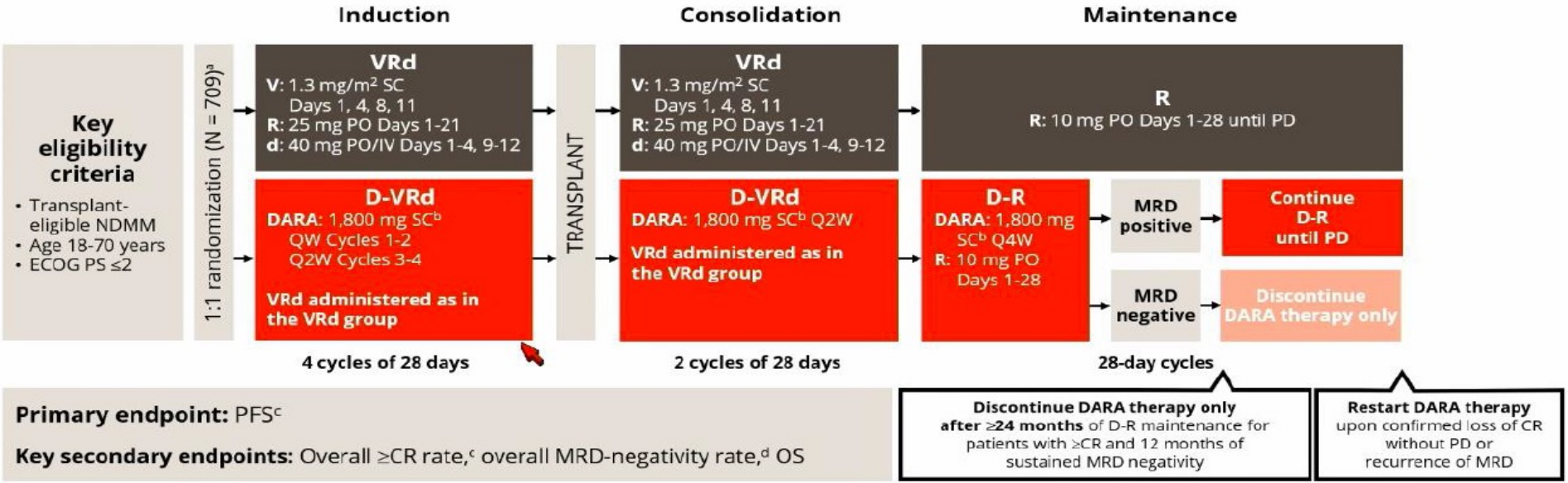




(A) The results of the Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population. (B) The results of the Kaplan–Meier estimates of overall survival among patients in the intention-to-treat population.
D-VTd=daratumumab, bortezomib, thalidomide, and dexamethasone. HR=hazard ratio. VTd=bortezomib, thalidomide, and dexamethasone.

Moreau et al. The Lancet Oncology 2024

DaraVRD vs VRD in TE NDMM: Phase 3 randomized Perseus trial study design (mean follow up 47.5 month)

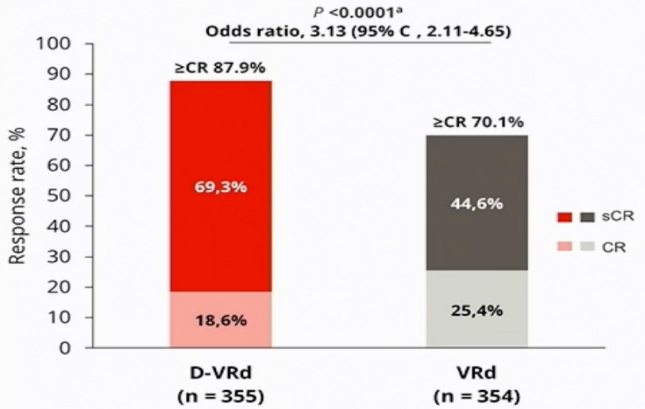


Sonneveld P et al NEJM Dec 2023

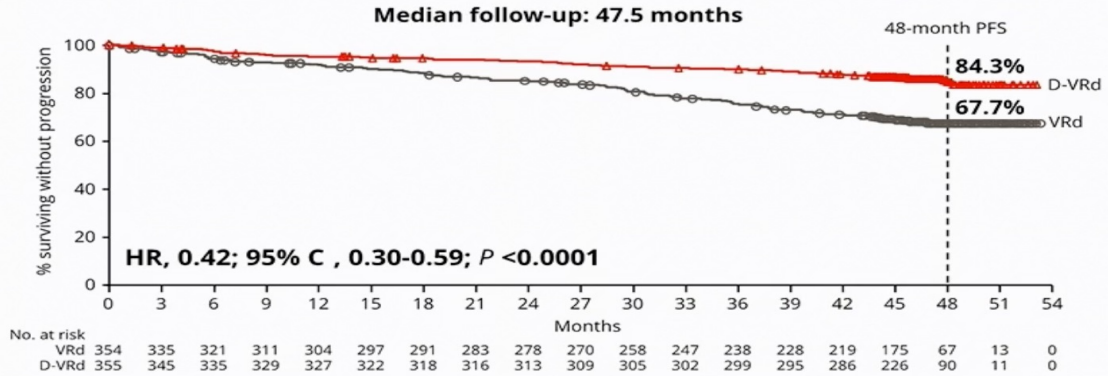
Dara-VRd vs VRd in TE NDMM: Phase 3 randomized PERSEUS trial
Key efficacy data (Median follow-up: 47.5 months)

D-VRD vs VRD
Median age: 61y vs 59y
ISS III: 15.5% vs 14.2%
HR-CA: 21.4% vs 22%

Overall ≥ CR rate D-VRd vs VRD



Progression-free survival



- **58% reduction in the risk of progression or death in patients receiving D-VRd**

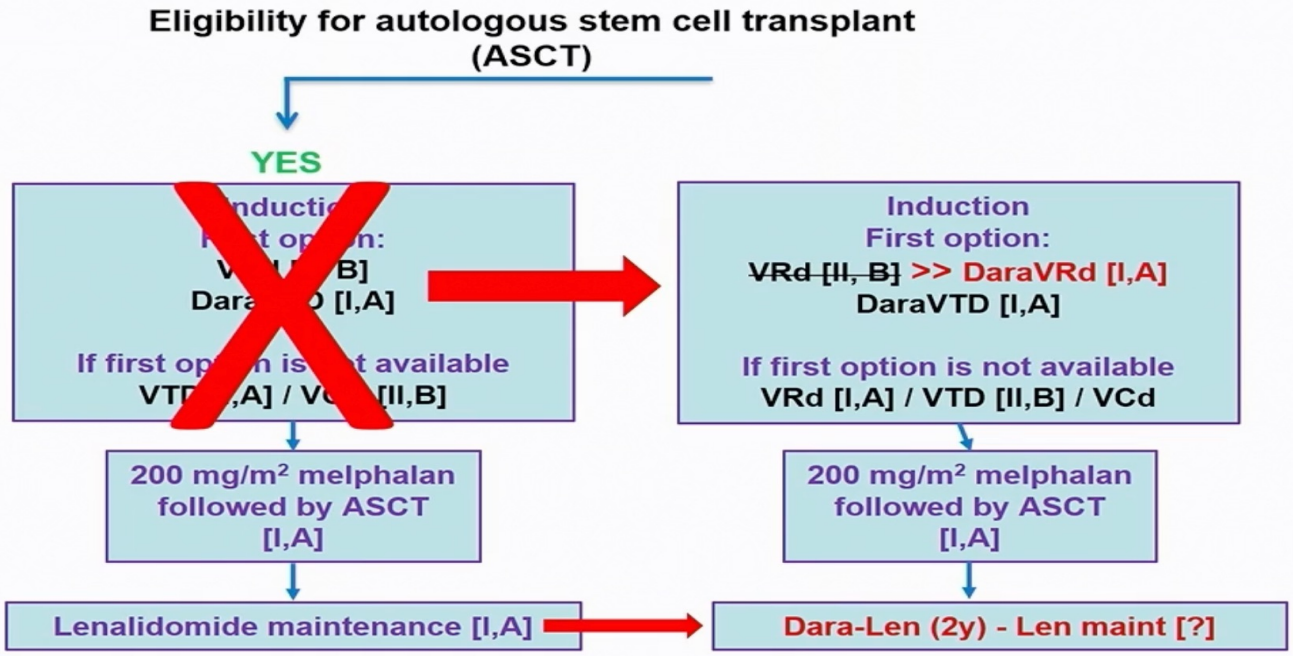
sCR, stringent complete response; NE, not estimable. [a]*P* value (2-sided) was calculated with the use of the stratified Cochran–Mantel–Haenszel chi-squared test.

Sonneveld P et al, ASH 2023, LBA oral presentation
Sonneveld P et al, NEJM Dec 2023

Due grandi novità:

1) Dara Len based maintenance
2) MRD driven maintenance

Front-line treatment of active MM outside clinical trials
Future EHA-ESMO 2025 guidelines



Dimopoulos MA et al. HemaSphere 2021, 5:2(e528)

Front-line treatment of active MM outside clinical trials
Future EHA-ESMO 203??

Eligibility for autologous stem cell transplant (ASCT)

YES

Induction
First option:
DaraVRd
DaraVTD [I,A]

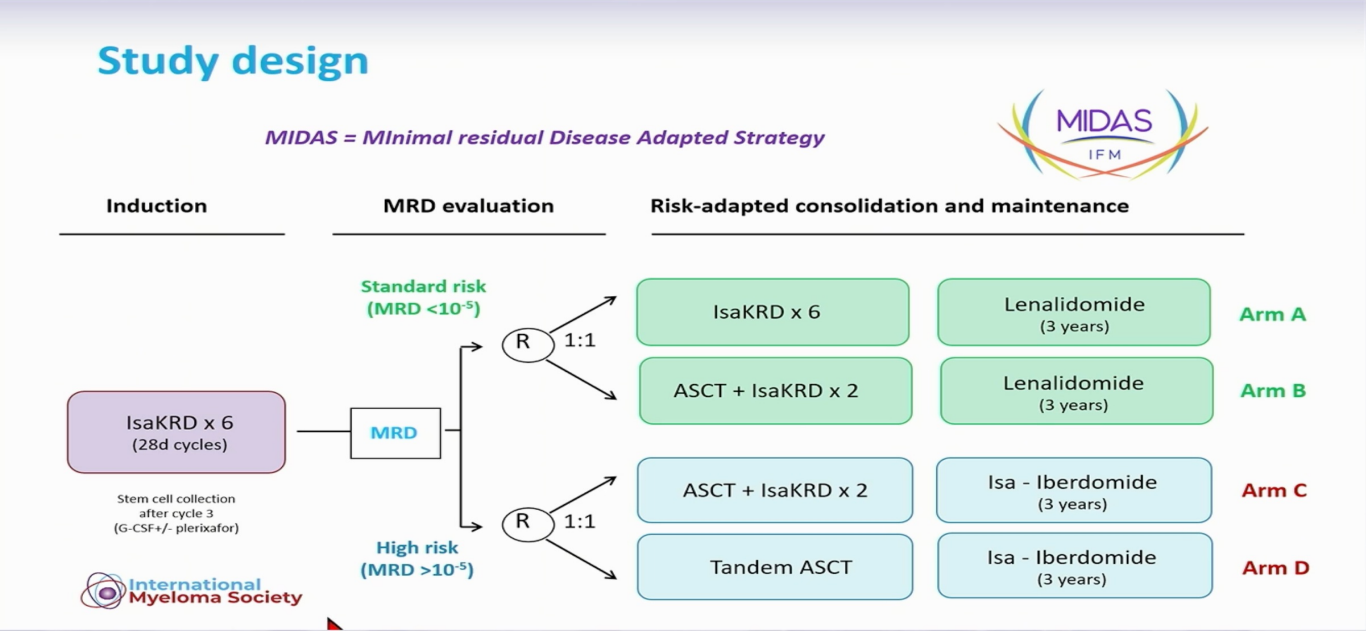
If first option is not available
VRd [I,A] / VTD [II,B] / VCd

Mel200 anymore?

*pending readout of future clinical trials

Dimopoulos MA et al. HemaSphere 2021, 5:2(e528)

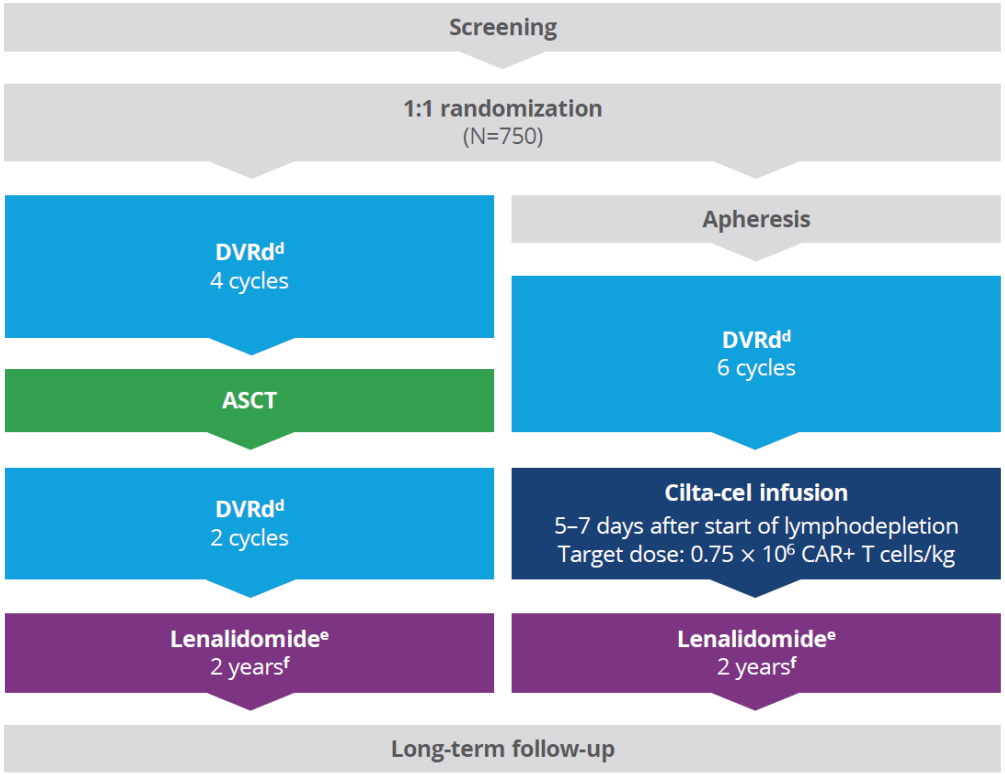
MIDAS: transplant MRD driven
Cartitude 6: no more transplant



92% VGPR or better; 64% CR; MRD neg: 63% 10^{-5}/ 47% 10^{-6}

IMS 2024

Cartitude 6 study design



Cook G et al. British Society for Haematology Annual Meeting; 23–25 April 2023; Birmingham,

Front-line treatment of active MM outside clinical trials
Future EHA-ESMO 203??

Eligibility for autologous stem cell transplant (ASCT)

YES

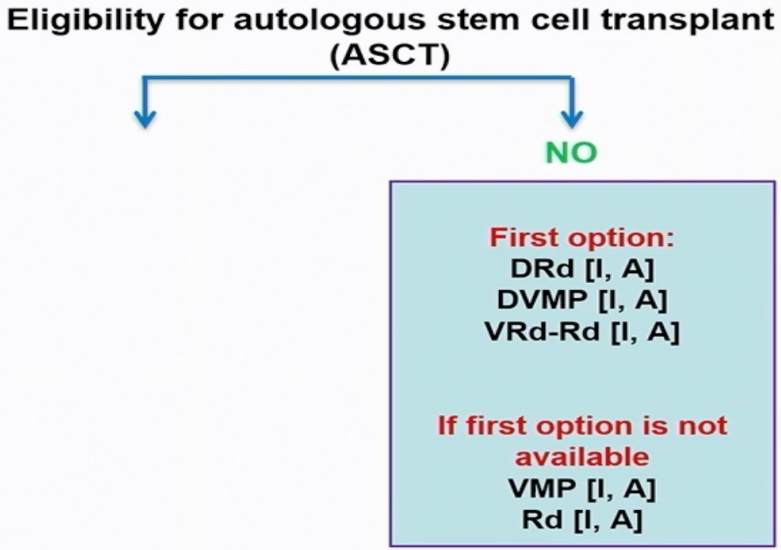
Induction
First option:
DaraVRd
DaraVTD [I,A]

If first option is not available
VRd [I,A] / VTD [II,B] / VCd

*pending readout of future clinical trials

Dimopoulos MA et al. HemaSphere 2021, 5:2(e528)

Front-line treatment of TNE-NDMM outside clinical trials
EHA-ESMO guidelines 2021

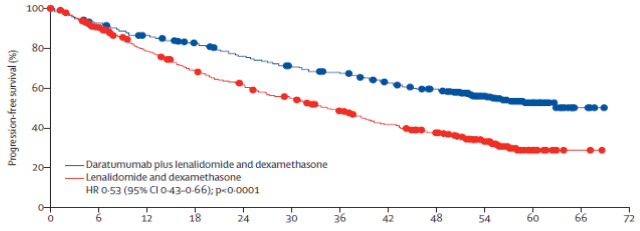


Dimopoulos MA et al. HemaSphere 2021, 5:2(e528)

Daratumumab plus lenalidomide and dexamethasone for patients with TIE NDMM: the standard of care

MAIA trial

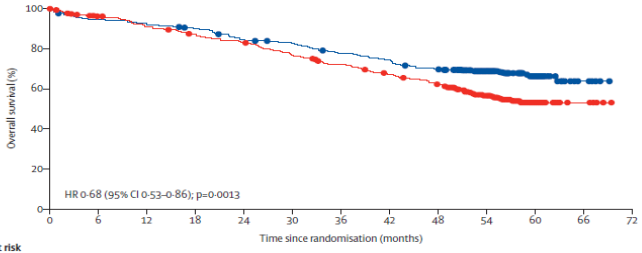
PFS[1]



Number at risk (number censored)

Lenalidomide and dexamethasone	369 (0)	307 (29)	255 (41)	220 (44)	196 (46)	172 (49)	146 (55)	123 (58)	105 (64)	63 (95)	12 (140)	2 (150)	0 (152)
Daratumumab plus lenalidomide and dexamethasone	368 (0)	335 (6)	309 (9)	290 (14)	266 (16)	246 (18)	232 (20)	210 (25)	195 (30)	123 (92)	51 (158)	5 (203)	0 (208)

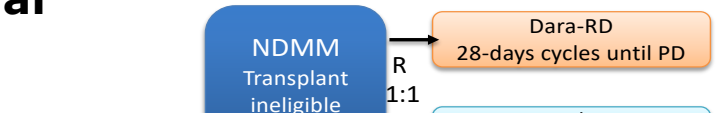
OS[1]



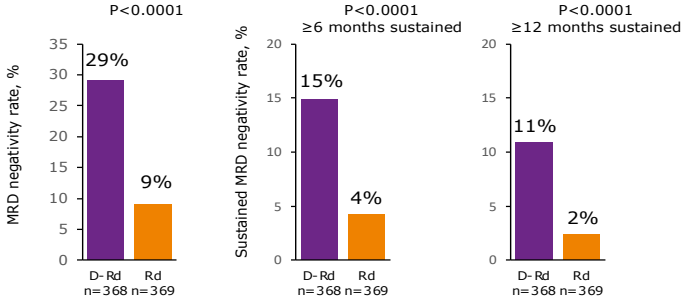
Number at risk (number censored)

Lenalidomide and dexamethasone	369 (0)	343 (13)	324 (14)	308 (16)	294 (16)	270 (17)	251 (20)	232 (22)	213 (24)	134 (85)	42 (171)	5 (208)	0 (213)
Daratumumab plus lenalidomide and dexamethasone	368 (0)	346 (3)	338 (3)	328 (5)	305 (6)	297 (8)	280 (9)	266 (9)	249 (10)	170 (86)	63 (189)	6 (245)	0 (251)

Median PFS 62 months



MRD negativity rate[2]



CI, confidence intervals; CrCl, creatinine clearance; D-Rd, daratumumab-lenalidomide-dexamethasone; FU, follow-up; HR, hazard ratio; ISS, international staging system; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide-dexamethasone; TIE, transplant-ineligible

1. Facon T et al. Lancet Oncol 2021;22:1582–1596
2. San-Miguel J et al. Blood 2022;139(4):492–501

Phase III studies are investigating CD38 mAb-based quadruplet therapy using various dosing schedules in Ti NDMM

IMROZ[1,2]

N=446
- ✓ **Ti NDMM**
- ✓ 18–80 years
- × ECOG PS >2

3:2

Initiation (6-week cycles) → Maintenance phase (4-week cycles)

- **Isa-VRd** x4 cycles → **Isa-Rd**
- **VRd** x4 cycles → **Rd**

Until PD, unacceptable toxicity, or patient withdrawal

Primary endpoint: PFS

Isa IV: 10 mg/kg weekly (C1), every 2 weeks (C2–17), monthly (C18+)
V SC: 1.3 mg/m² **twice-weekly** (W1–2 and 4–5 of C1–4) during initiation only
d IV/PO: 20 mg during C1–17* then **weekly** (C18+)

BENEFIT[3–5]

N=270
- ✓ **Ti NDMM**
- ✓ 65–79 years
- × ECOG PS >2

1:1

Induction (4-week cycles)

- **Isa-VRd** x12 cycles → **Isa-VR** x6 cycles → **Isa-R**
- **Isa-Rd** x12 cycles → **Isa-R** x6 cycles → **Isa-R**

Until PD, unacceptable toxicity, or patient withdrawal

Primary endpoint: MRD– (10^{-5})

Isa IV: 10 mg/kg weekly (C1), every 2 weeks (C2–12), monthly (C13+)
V SC: 1.3 mg/m² **weekly** (W1–3 of C1–12) and then **every 2 weeks** (C13–18)
d PO: 20 mg **weekly** (C1–12) then discontinued

*Administered on Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33, or on Days 1, 4, 8, 11, 15, 22, 25, 29, and 32 in patients aged ≥75 years.
C, cycle; d, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Isa, isatuximab; IV, intravenous; mAb, monoclonal antibody; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PFS, progression-free survival; PO, orally; R, lenalidomide; SC, subcutaneous; Ti, transplant ineligible; V, bortezomib; W, week

1. Facon T, et al. N Engl J Med 2024; doi: 10.1056/NEJMoa2400712. Online ahead of print;
2. Clinicaltrials.gov. NCT03319667;
3. Leleu X, et al. Nature 2024;
4. Clinicaltrials.gov. NCT04751877;
5. Leleu X, et al. ASCO 2024; Presentation 7501

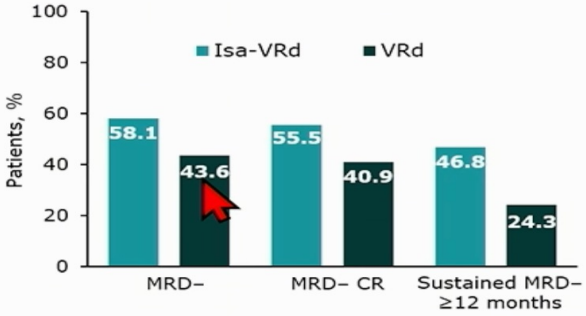
As no head-to-head comparisons are available, direct comparison between trials is not intended and should not be inferred

IMROZ: First global Phase III study of Isa-VRd vs VRd in Ti NDMM

IMROZ: Isa-VRd vs VRd (N=446) in Ti NDMM

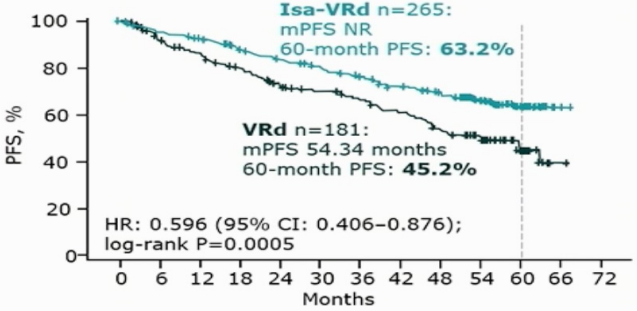
Isa IV: 10 mg/kg weekly (C1), every 2 weeks (C2–17), monthly (C18+)
V SC: 1.3 mg/m² **twice-weekly** (W1–2 and 4–5 of C1–4) during initiation only
d IV/PO: **20 mg** during C1–17* then **weekly** (C18+)

MRD– rates (NGS, 10^{-5}; ITT)



Median follow-up: 5 years

Primary endpoint: PFS (ITT)



OS rates (ITT)

	Isa-VRd	VRd
60-month OS rate, %	72.3	66.3
HR (95% CI)	0.776 (0.407–1.48)	

At a median follow-up of 5 years, Isa-VRd followed by Isa-Rd resulted in a statistically significant reduction in the risk of progression or death by 40.4% and in consistent deep responses vs VRd followed by Rd. The 60-month PFS and OS rates highlight the PFS and OS benefit of Isa-VRd vs VRd in Ti NDMM patients

*Administered on Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33, or on Days 1, 4, 8, 11, 15, 22, 25, 29, and 32 in patients aged ≥75 years.
C, cycle; CI, confidence interval; CR, complete response; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ITT, intention-to-treat; IV, intravenous; m, median; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; NR, not reached; OS, overall survival; PFS, progression-free survival; PO, orally; R, lenalidomide; SC, subcutaneous; Ti, transplant ineligible; V, bortezomib; W, week

1. Facon T, et al. N Engl J Med 2024; doi: 10.1056/NEJMoa2400712. Online ahead of print;
2. Facon T, et al. ASCO 2024; Presentation 7500

Cepheus: Phase III protocol of DVRD vs VRD in patients TI or transplant deferred

CEPHEUS[1,2]

N=395
- ✓ **Ti or transplant-deferred NDMM**
- ✓ ≥18 years
- × ECOG PS >2
- × Frailty score ≥2*

1:1

Induction (3-week cycles)
- **DVRd** x8 cycles
- **VRd** x8 cycles

Continuous phase (4-week cycles)
- **DRd**
- **Rd**

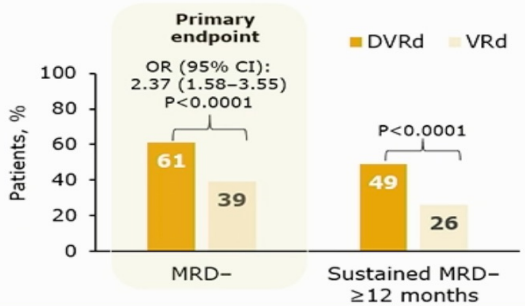
Until PD or unacceptable toxicity

Primary endpoint: MRD− (10^{-5})

Dara SC: 1800 mg weekly (C1–2), every 3 weeks (C3–8), monthly (C9+)
V SC: 1.3 mg/m² twice-weekly (W1–2 of C1–8); then discontinued
d PO: 20 mg during C1–8† then 40 mg weekly for C9+

Median follow-up: 58.7 months

MRD− rates (NGS, 10^{-5})



PFS

	DVRd (n=197)	VRd (n=198)
mPFS, months	NR	52.6
HR (95% CI)	0.57 (0.41–0.79)	
P-value	0.0005	
54-month PFS rate, %	68.1	49.5

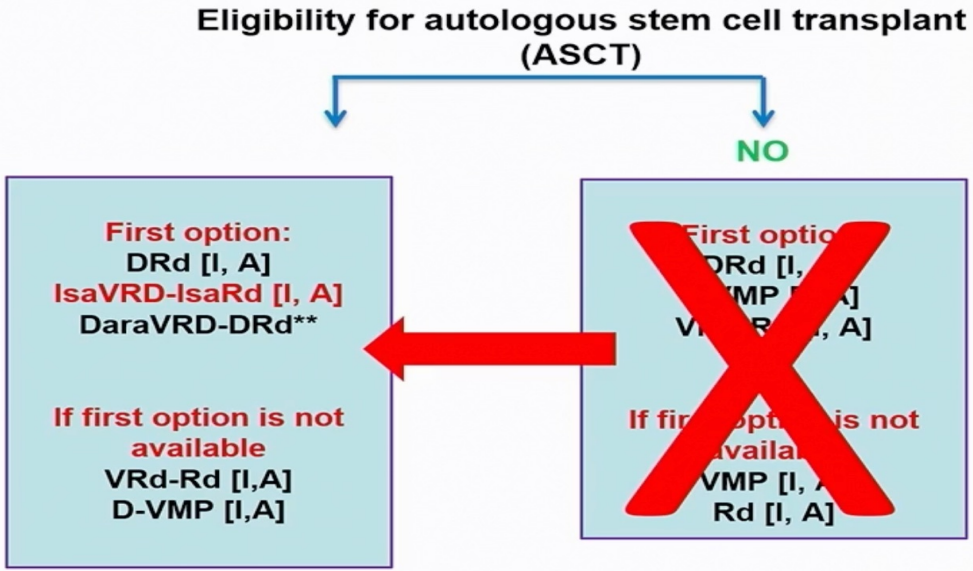
Safety

	DVRd	VRd
Median treatment duration, months	56.3	34.3
Grade 5 TEAE rates,‡ per 100 patient-months	0.39	0.31

DVRd significantly increased overall MRD negativity (primary endpoint) and sustained MRD negativity vs VRd, and also significantly improved PFS, reducing the risk of progression or death by 43%

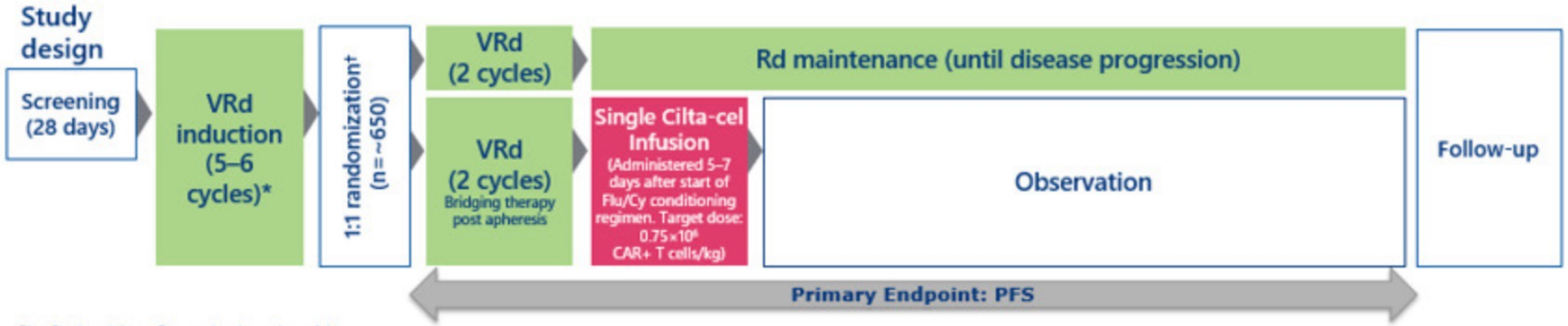
Usmani IMS 2024

Front-line treatment of active MM outside clinical trials
Future EHA-ESMO guidelines 2025



Dimopoulos MA et al. HemaSphere 2021, 5:2(e528)

Figure: CARTITUDE-5 study design

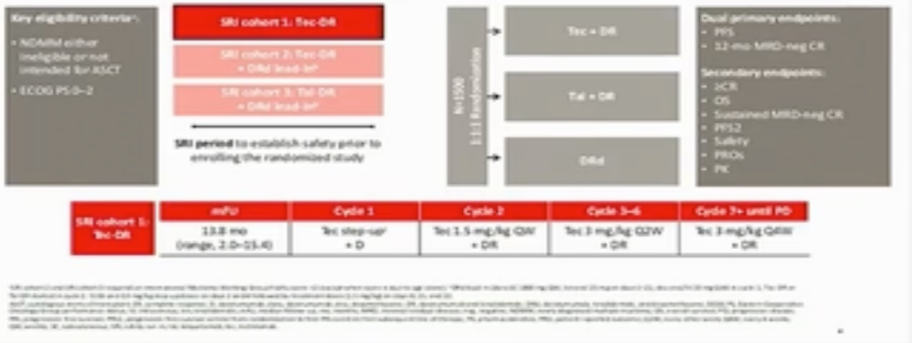


Flu, fludarabine; Cy, cyclophosphamide
*1 cycle VRd allowed prior to screening
†Stratification factors: R-ISS (I,II,III); Age/transplant eligibility (≥70 years or <70 years and ASCT ineligible due to comorbidities or <70 years and ASCT deferred); Response to VRd induction (≥VGPR, ≤PR)

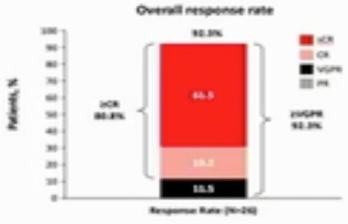
Future Perspectives

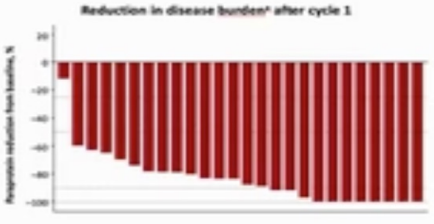
MajesTEC-7 – Phase 3 NDMM – Tec-DR vs Tal-DR vs DRd

MajesTEC-7: SRI Cohorts Inform Phase 3 Design



MajesTEC-7 (Tec-DR) SRI Cohort 1: Efficacy





- 92.3% ORR (80.8% ≥CR); all responses were ≥VGPR
- No disease progressions

- Median time to first response: 1.0 month (range, 0.9–4.6)
- Median time to best response: 6.5 months (range, 1.0–12.1)

Cyrille Touzeau, et al. ASCO 2024

Front-line treatment of active MM outside clinical trials
Future EHA-ESMO guidelines 2030…

Eligibility for autologous stem cell transplant (ASCT)

NO

First option:
DRd [I, A]
DVMP [I, A]
VRd-Rd [I, A]

If first option is not available
VMP [I, A]
Rd [I, A]

First option:
DRd [I, A]
IsaVRD-IsaRd [I, A]
DaraVRD-DRd

If first option is not available
VRd-Rd [I,A]
D-VMP [I,A]

First option:
~~DRd [I, A]~~ >> ElranDR* or TecDR* or BelaRd*

IsaVRD-IsaRd [I, A]
DaraVRD-DRd

VRD + Cilta-cel* (CARTITUDE-5)

If first option is not available
DRd (frail) [I,A]
D-VMP [I,A]
[very frail: doublets]

*pending readout of future clinical trials

Dimopoulos MA et al. HemaSphere 2021, 5:2(e528)

Treatment at relapse outside clinical trials
Current EHA-ESMO guidelines 2021

1st line

ASCT eligible

Anti CD38 + PI + IMID + Dex
ASCT
Len/Dara or Len

ASCT ineligible

Dara + Len-dex
Dara-VMP
AntiCD38 + VRd

progress while on lenalidomide and/or daratumumab

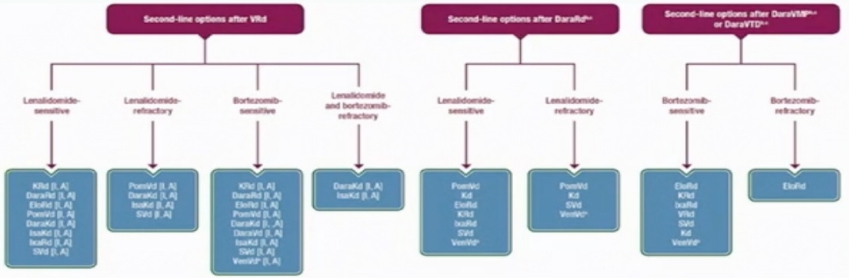
2nd line

Prior antiCD38 and/or Len exposure/refractoriness

Dara/Isa + Kd (or ~~Vd~~)

Dara/Isa + Pd

Pomalidomide-bortezomib-dex
Carfilzomib-dex
Selinexor-bortezomib-dex



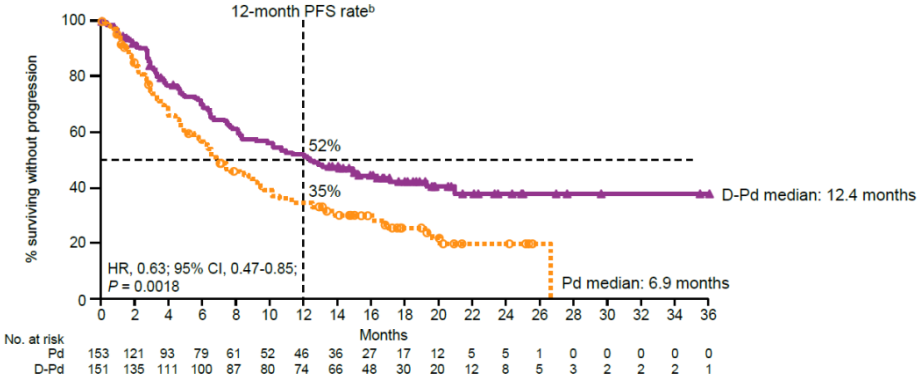
In 2L patients not exposed to Len or Dara >> DRd
In 2L patients Dara-Ref but Len naive >> Rd or KRd

ASCT: autologous stem cell transplant; PI: proteasome inhibitor; IMID: immunomodulatory agent; Dex: dexamethasone; VMP: bortezomib, melphalan, prednisone, VRD: bortezomib, lenalidomide, dexamethasone; Len: lenalidomide; Kd: carfilzomib-dexamethasone; Pd: pomalidomide, dexamethasone; PVd: pomalidomide, bortezomib, dexamethasone; DRd: daratumumab, lenalidomide, dexamethasone; KRd: carfilzomib, lenalidomide, dexamethasone, Tec: teclistamab, Tal: talquetamab; Elra: elranatamab; Pd: pomalidomide, dexamethasone; Vd: bortezomib, dexamethasone

Data presented from multiple trials for convenience. Comparisons cannot be made between safety and/or efficacy parameters across studies. Cross-trial comparisons are not to be inferred.

Based on: Dimopoulos MA, et al. Ann Oncol 2021;32:309-322. Kaufman J et al. ASH 2019; abstract 1866 (poster presetnation). Avet-Loiseau H et al. Blood Cancer J 2020;(11):111.

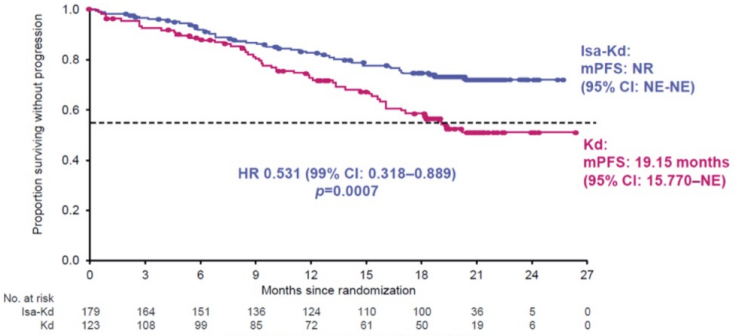
APOLLO: DaraPd > Pd (response, PFS)
≥1 prior line, lena and PI exposed

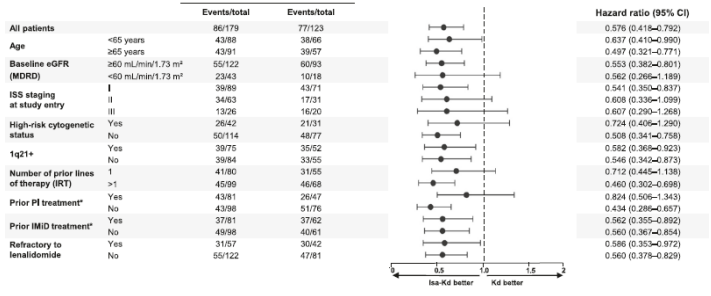


DaraPD
PFS: 12.4 m (9.9 m len-refractory), HR: 0.63
CR 25%

1-3 prior lines of therapy
30% len-refractory

IKEMA (Median follow-up: 44 months)
ISATUXIMAB + Kd > Kd (response, PFS)

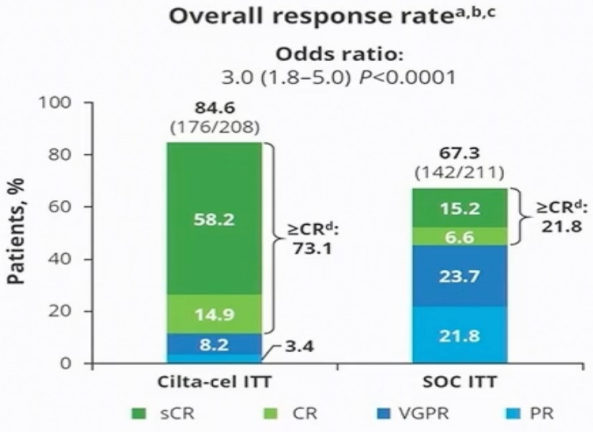




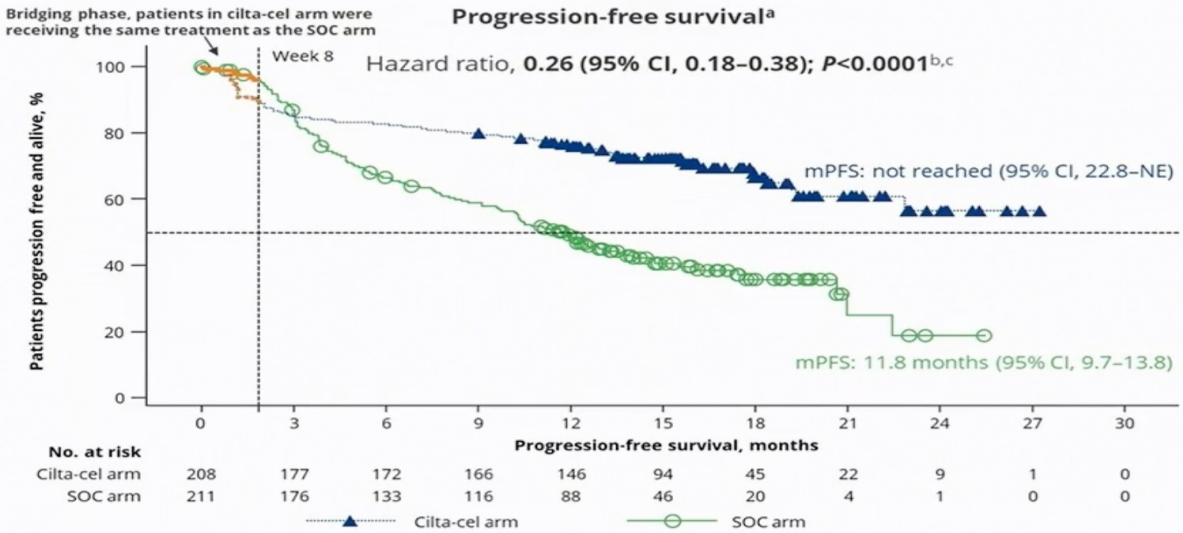
CARTITUDE-4: Phase 3 randomized Cilta-cel vs SoC in 1-3 RRMM Len-Ref

Median FUP: 15.9 m

- Cilta-cel: **median nº PL: 2 (1-3)**, 1 PL in 32.7%; HR-CA 35.3%; Dara-Ref 23.1; **TCE 25.5%**
- SoC (DPd/PVd): **median nº PL 2 (1-3);** 1 PL 32.2%; HR-CA 32.9%; Dara-Ref 21.3%; **TCE 26.1%**



MRD neg (10^{-5}) in pts evaluable for MRD: Cilta-cel 87.5% vs SoC 32.7%

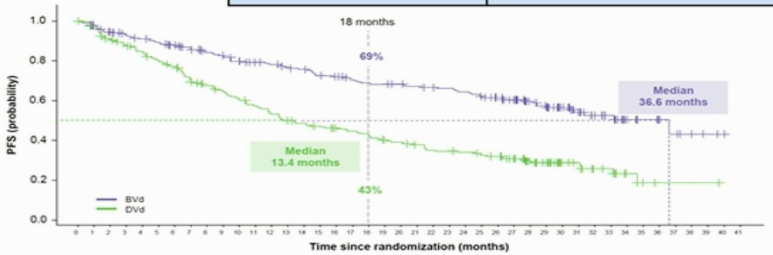


HR by COX: 0.4

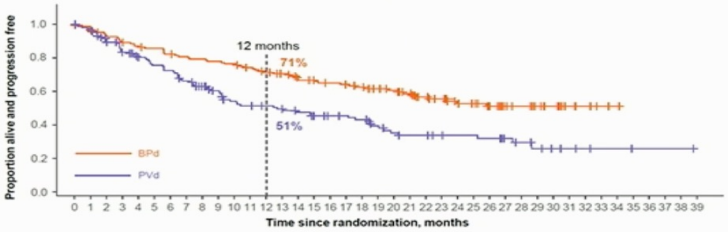
Dakhal B et al. J Clin Oncol 41, 2023 (suppl 17; abstr LBA106)
Einsele H et al, plenary session, EHA 2023

Belantamab-based combinations in Len/αCD38-refractory patients

DREAMM-7	BVd (n=243)	DVd (n=251)
PFS (mo)(95% CI)	36.6 (28.4-NR)	13.4 (11.1-17.5)
HR	0.41 (0.31-0.53) p<0.001	



DREAMM-8	BPd (n=155)	PVd (n=147)
PFS (mo)(95% CI)	NR (20.6-NR)	12.7 (9.1-18.5)
HR	0.52 (0.37-0.73) p<0.001	



Prior Tx/refractoriness	No previous Dara exposure (1-2% exposed, in fact)	23-24% anti-CD38 refractory
	86-90% PI exposed	24-26% PI refractory
	34% Len refractory	76-81% Len refractory
	81-86% iMid exposed	100% iMid exposed
Prior lines	51% had 1 prior line	52-53% had 1 prior line
PFS (m); HR-Len refractory	25.0 (18.1-NR); HR 0.37 (0.24-0.56)	HR 0.45 (0.31-0.65)
PFS (m); HR – anti-CD38 refractory	N/A	HR 0.65 (0.36-1.18)

Hungria V et al. *NEJM* 2024; 391:393-407; Dimopoulos MA et al. *NEJM* 2024; 391:408-21

Treatment at first relapse outside clinical trials
Future EHA-ESMO guidelines 2025

1st line

ASCT eligible

Anti CD38 + PI + IMID + Dex
ASCT
Len/Dara or Len

ASCT ineligible

Dara + Len-dex
Dara-VMP
AntiCD38 + VRd

progress while on lenalidomide and/or daratumumab

2nd line

Prior antiCD38 and/or Len exposure/refractoriness

Dara/Isa + Kd
Dara/Isa + Pd

Pomalidomide-bortezomib-dex
Carfilzomib-dex
Selinexor-bortezomib-dex

Cilta-Cel [I,A]
*Belantamab-Vd**
*Belantamab-Pd**

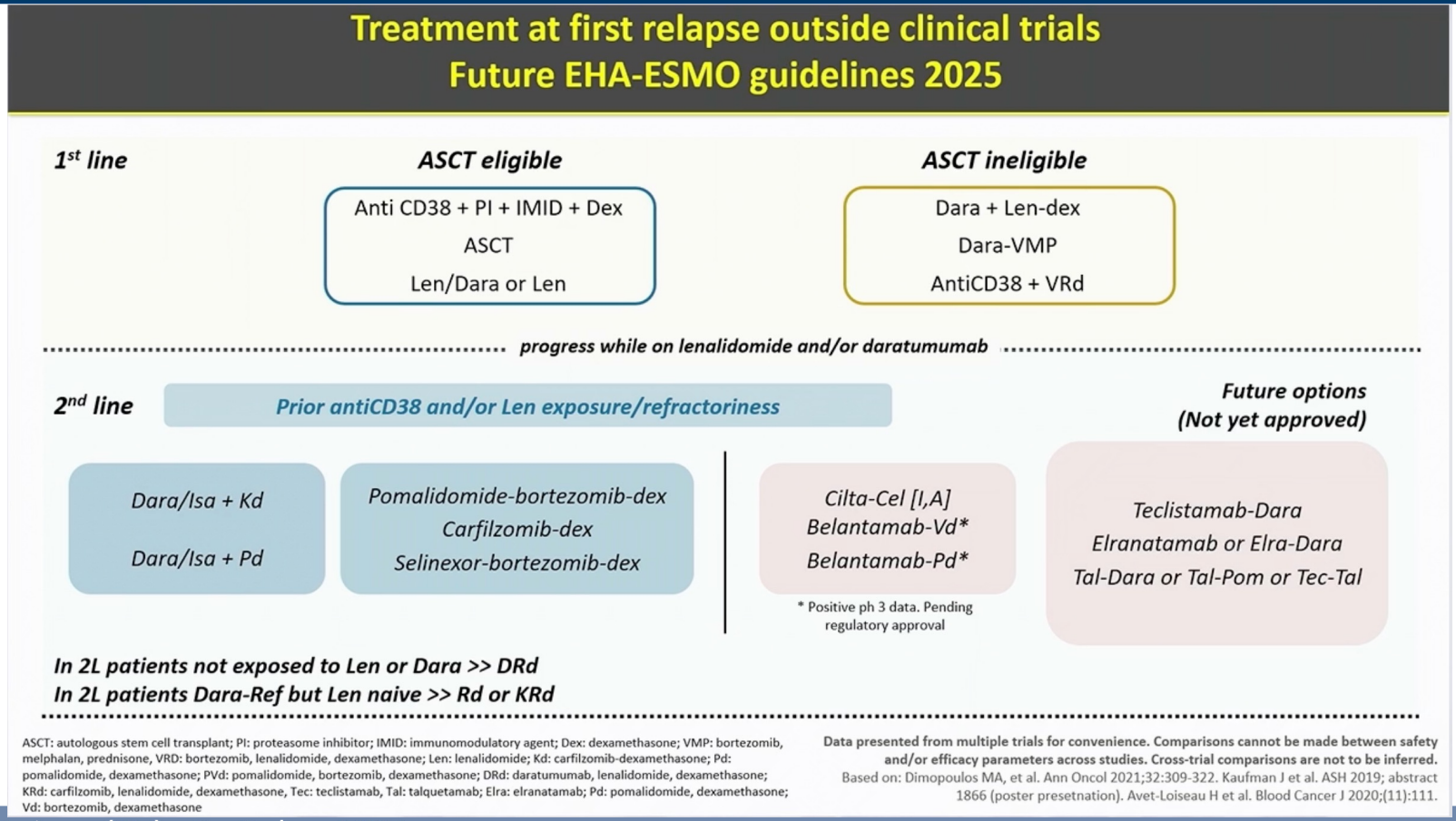
* Positive ph 3 data. Pending regulatory approval

In 2L patients not exposed to Len or Dara >> DRd
In 2L patients Dara-Ref but Len naive >> Rd or KRd

ASCT: autologous stem cell transplant; PI: proteasome inhibitor; IMID: immunomodulatory agent; Dex: dexamethasone; VMP: bortezomib, melphalan, prednisone, VRD: bortezomib, lenalidomide, dexamethasone; Len: lenalidomide; Kd: carfilzomib-dexamethasone; Pd: pomalidomide, dexamethasone; PVd: pomalidomide, bortezomib, dexamethasone; DRd: daratumumab, lenalidomide, dexamethasone; KRd: carfilzomib, lenalidomide, dexamethasone, Tec: teclistamab, Tal: talquetamab; Elra: elranatamab; Pd: pomalidomide, dexamethasone; Vd: bortezomib, dexamethasone

Data presented from multiple trials for convenience. Comparisons cannot be made between safety and/or efficacy parameters across studies. Cross-trial comparisons are not to be inferred.

Based on: Dimopoulos MA, et al. Ann Oncol 2021;32:309-322. Kaufman J et al. ASH 2019; abstract 1866 (poster presetnation). Avet-Loiseau H et al. Blood Cancer J 2020;(11):111.


Treatment at first relapse outside clinical trials
Future EHA-ESMO guidelines 2025
1st line
ASCT eligible
Anti CD38 + PI + IMID + Dex
ASCT
Len/Dara or Len
ASCT ineligible
Dara + Len-dex
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2nd line
Prior antiCD38 and/or Len exposure/refractoriness
Dara/Isa + Kd
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Pomalidomide-bortezomib-dex
Carfilzomib-dex
Selinexor-bortezomib-dex
Cilta-Cel [I,A]
Belantamab-Vd*
Belantamab-Pd*
* Positive ph 3 data. Pending regulatory approval
Future options
(Not yet approved)
Teclistamab-Dara
Elranatamab or Elra-Dara
Tal-Dara or Tal-Pom or Tec-Tal
In 2L patients not exposed to Len or Dara >> DRd
In 2L patients Dara-Ref but Len naive >> Rd or KRd
ASCT: autologous stem cell transplant; PI: proteasome inhibitor; IMID: immunomodulatory agent; Dex: dexamethasone; VMP: bortezomib, melphalan, prednisone, VRD: bortezomib, lenalidomide, dexamethasone; Len: lenalidomide; Kd: carfilzomib-dexamethasone; Pd: pomalidomide, dexamethasone; PVd: pomalidomide, bortezomib, dexamethasone; DRd: daratumumab, lenalidomide, dexamethasone; KRd: carfilzomib, lenalidomide, dexamethasone, Tec: teclistamab, Tal: talquetamab; Elra: elranatamab; Pd: pomalidomide, dexamethasone; Vd: bortezomib, dexamethasone
Data presented from multiple trials for convenience. Comparisons cannot be made between safety and/or efficacy parameters across studies. Cross-trial comparisons are not to be inferred.
Based on: Dimopoulos MA, et al. Ann Oncol 2021;32:309-322. Kaufman J et al. ASH 2019; abstract 1866 (poster presetnation). Avet-Loiseau H et al. Blood Cancer J 2020;(11):111.

Treatment at 2nd relapse and beyond outside clinical trials
Current EHA-ESMO 2021 guidelines

1st line

ASCT eligible

Anti CD38 + PI + IMID + Dex
ASCT
Len/Dara or Len

ASCT ineligible

Dara + Len-dex
Dara-VMP/RVd
AntiCD38 + VRd

2nd line

Prior antiCD38 and/or Len exposure/refractoriness

Anti CD38 + Kd
Anti CD38 + Pd

Pomalidomide-bortezomib-dex
Carfilzomib-dex
Selinexor-bortezomib-dex

In 2L patients not exposed to Len or Dara >> DRd
In 2L patients Dara-Ref but Len naive >> Rd or KRd

Future options

Cilta-Cel
Belantamab-Vd
Belantamab-Pd

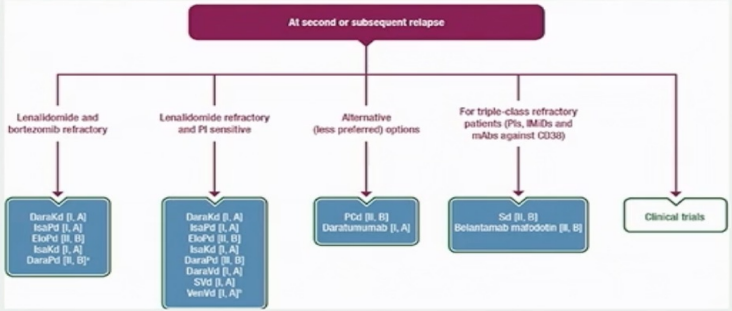
* Positive ph 3 data. Pending regulatory approval

Teclistamab-Dara
Elranatamab or Elra-Dara
Tal-Dara or Tal-Pom or Tec-Tal

3rd line and beyond

Recycle prior options if posible

Isatuximab-Pom-Dex
Elotuzumab-Pom-Dex



ASCT: autologous stem cell transplant; PI: proteasome inhibitor; IMID: immunomodulatory agent; Dex: dexamethasone; VMP: bortezomib, melphalan, prednisone, VRD: bortezomib, lenalidomide, dexamethasone; Len: lenalidomide; Kd: carfilzomib-dexamethasone; Pd: pomalidomide, dexamethasone; PVd: pomalidomide, bortezomib, dexamethasone; DRd: daratumumab, lenalidomide, dexamethasone; KRd: carfilzomib, lenalidomide, dexamethasone, Tec: teclistamab, Tal: talquetamab; Elra: elranatamab; Pd: pomalidomide, dexamethasone; Vd: bortezomib, dexamethasone

Data presented from multiple trials for convenience. Comparisons cannot be made between safety and/or efficacy parameters across studies. Cross-trial comparisons are not to be inferred.

Based on: Dimopoulos MA, et al. Ann Oncol 2021;32:309-322. Kaufman J et al. ASH 2019; abstract 1866 (poster presetnation). Avet-Loiseau H et al. Blood Cancer J 2020;(11):111.

Ph 3 KarMMa-3: ide-cel vs SoC in TCE RRMM (2-4 prior lines)
Final PFS analysis and OS data (mFUP 31 m)

Key elegibility: 2-4 PL. Triple-class exposed. Refractory to last line.
Baseline characteristics were comparable between 2 arms:

- Median nº of PL: 3
- Median time from diagnosis to study entry 4 years.
- 65% of patients in both arms were triple-class refractory
- Median TTP in last regimen: 7 months

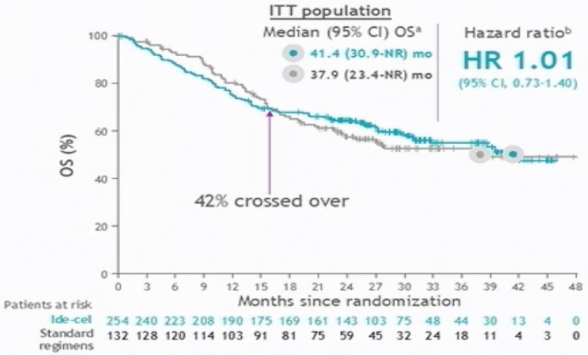
ORR 71% (CRR 44%) vs 42% (CRR 6%)

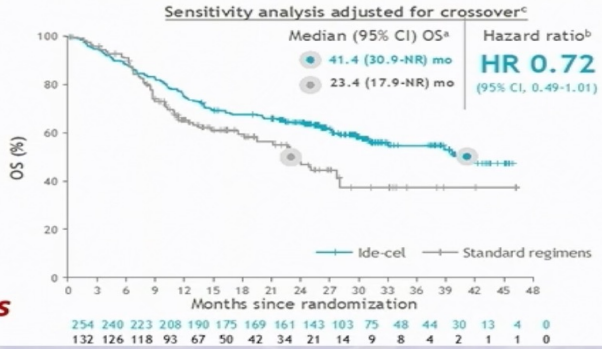
Final PFS analysis

- mDOR ide-cel (16.6m [12.0–18.6] vs SoC 9.7 [5.4–16.3] m)
- mTTR: 2.9 (0.5–13.0) vs 2.1 (0.9–9.4) months
- MRDneg CR: ide-cel 35% (57) vs SoC 2% (1)
- mPFS2 23.5 m vs 16.7 m [HR 0.79 (95% CI, 0.6 -1.04)]

Rodriguez-Otero P et al. oral presentation. ASH 2023. Abstract 1028

OS analysis (ITT and sensitivity análisis)





No new safety signlas

Treatment at 2nd relapse outside clinical trials
Current EHA-ESMO 2021 guidelines

1st line

ASCT eligible

Anti CD38 + PI + IMID + Dex
ASCT
Len/Dara or Len

ASCT ineligible

Dara + Len-dex
Dara-VMP/RVd
AntiCD38 + VRd

2nd line

Prior antiCD38 and/or Len exposure/refractoriness

Anti CD38 + Kd
Anti CD38 + Pd

Pomalidomide-bortezomib-dex
Carfilzomib-dex
Selinexor-bortezomib-dex

In 2L patients not exposed to Len or Dara >> DRd
In 2L patients Dara-Ref but Len naive >> Rd or KRd

Future options

Cilta-Cel
Belantamab-Vd
Belantamab-Pd

* Positive ph 3 data. Pending regulatory approval

Teclistamab-Dara
Elranatamab or Elra-Dara
Tal-Dara or Tal-Pom or Tec-Tal

3rd line

Recycle prior options if posible

Isatuximab-Pom-Dex
Elotuzumab-Pom-Dex

Ide-cel (K-3) [I,A]

ASCT: autologous stem cell transplant; PI: proteasome inhibitor; IMID: immunomodulatory agent; Dex: dexamethasone; VMP: bortezomib, melphalan, prednisone, VRD: bortezomib, lenalidomide, dexamethasone; Len: lenalidomide; Kd: carfilzomib-dexamethasone; Pd: pomalidomide, dexamethasone; PVd: pomalidomide, bortezomib, dexamethasone; DRd: daratumumab, lenalidomide, dexamethasone; KRd: carfilzomib, lenalidomide, dexamethasone, Tec: teclistamab, Tal: talquetamab; Elra: elranatamab; Pd: pomalidomide, dexamethasone; Vd: bortezomib, dexamethasone

Data presented from multiple trials for convenience. Comparisons cannot be made between safety and/or efficacy parameters across studies. Cross-trial comparisons are not to be inferred.

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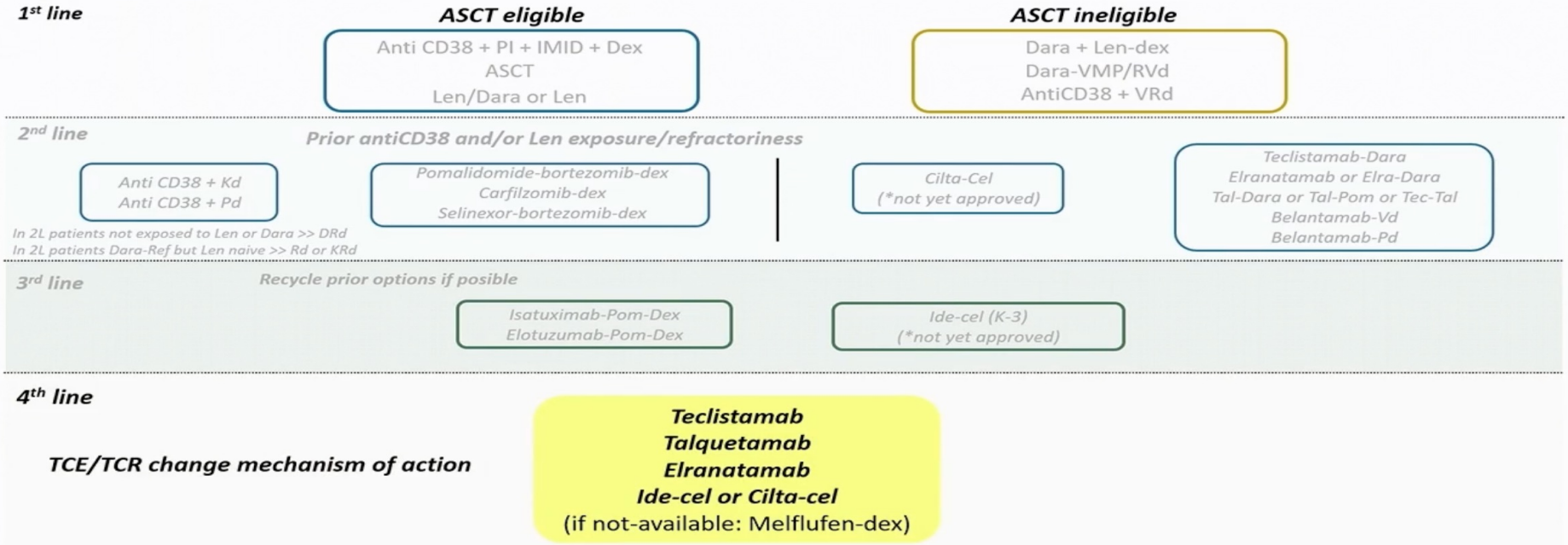
Treatment of Triple-class exposed RRMM
Future EHA-ESMO 2025 guidelines



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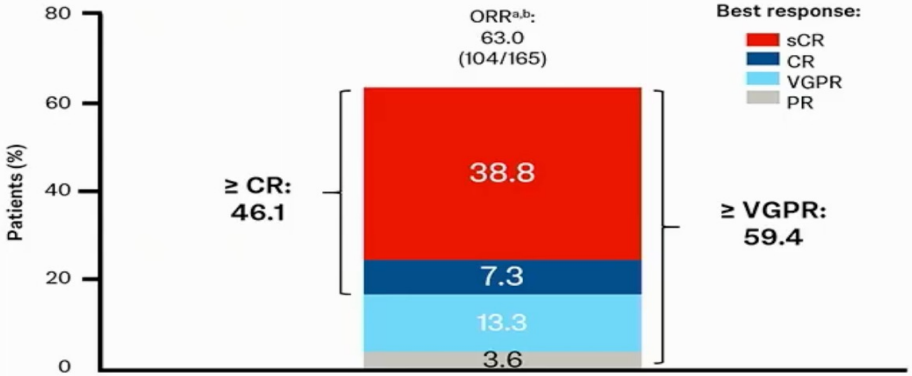
Teclistamab

Phase I/II MajesTEC-1: Teclistamab in R/R MM Long Term Outcomes

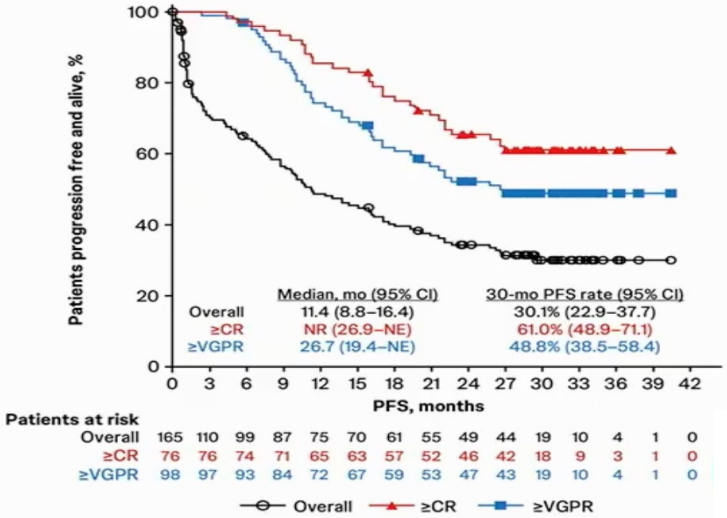
Teclistamab: 1.5 mg/kg SC weekly, after step-up



[a]Response assessed by independent review committee. [b]At 30-month mFU of the phase 2 efficacy population (patients enrolled in cohort A on or before March 18, 2021; n=110 patients supporting the USPI[c]): ORR, 61.8%; ≥CR, 46.4% (n=51).
sCR, stringent complete response; USPI, United States prescribing information.

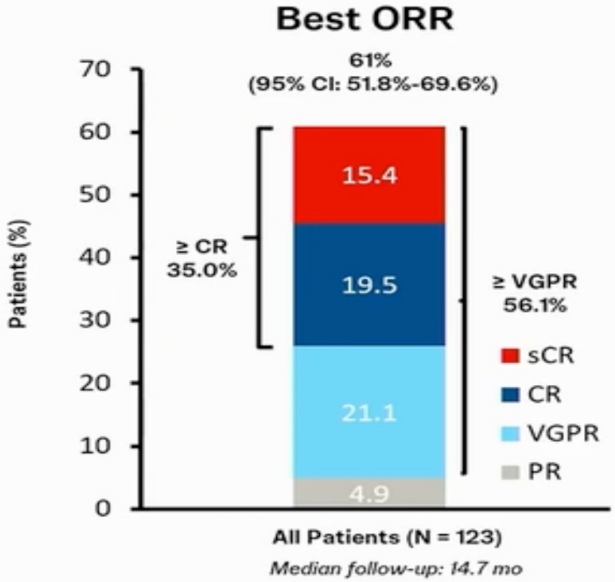
Deep and durable remissions associated with better DoR and PFS

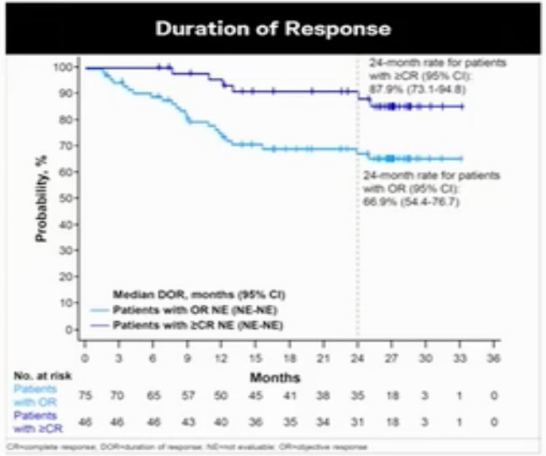
Outcomes, Mo (95% CI)	All Patients (N = 165)
Median DoR	24.0 (17.0-NE)
Median PFS	11.4 (8.8-16.4)
Median OS	21.9 (16-NE)

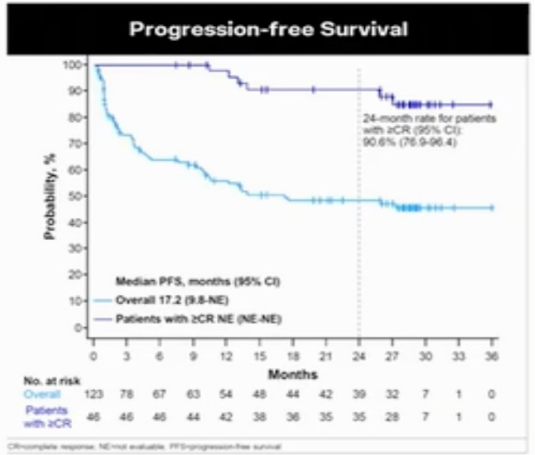


Moreau. NEJM. 2022;387:495. van de Donk. ASCO 2023. Abstr 8011. Garfall. ASCO 2024. Abstr 7540.

Long-Term Survival After Elranatamab Monotherapy in Patients With RRMM: MagnetisMM-3





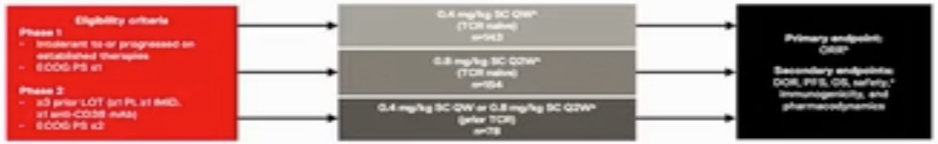


Mohty M *et al.* Abstract P906 Efficacy and safety of elranatamab monotherapy in the real-word setting in relapsed-refractory multiple myeloma (RRMM): results of the french compassionate use program on behalf of the IFM. Presentation at European Hematology Association 2024 annual meeting.

Talquetamab

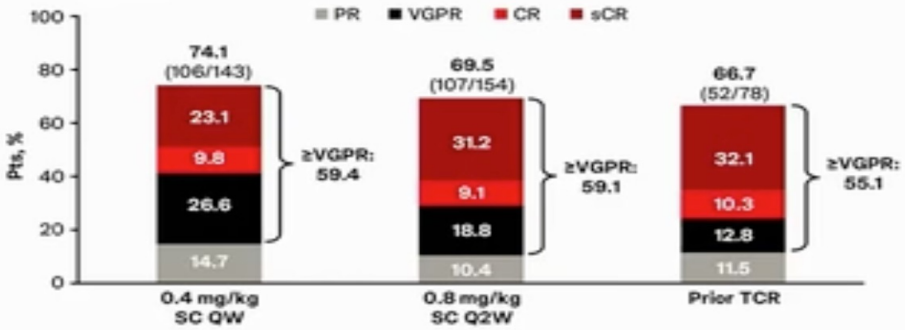
MonumenTAL-1: Long Term Outcomes

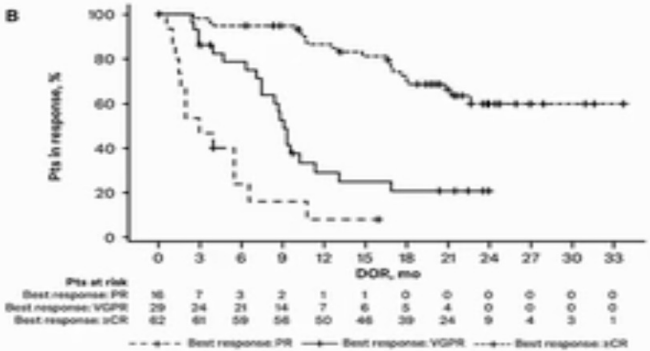
Figure 1: MonumenTAL-1 phase 1/2 study design



Outcome	0.4 mg/kg QW (n = 143)	0.8 mg/kg Q2W (n = 154)	Prior T-Cell Redirection Tx (n = 78)
Median f/u	29.8	23.4	20.5
Median DoR, mo (95% CI)	9.5 (6.7-13.4)	17.5 (12.5-NE)	N/A
Median PFS, mo (95% CI)	7.5 (5.7-9.4)	11.2 (8.4-14.6)	7.7 (4.1-14.5)
24-Mo OS, %	60.6	67.1	57.3

Figure 2: ORR[a]





Rasche L *et al.* Abstract P915 Long-term efficacy and safety results from the phase 1/2 monumenTAL-1 study of talquetamab, a GPRC5DxCD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma. Presentation at European Hematology Association 2024 annual meeting.

Nuove opportunità… nuove problematiche

MM 1 linea:
Necessità di definire con precisione pazienti che possano beneficiare di specifiche terapie.
Ruolo dell'autotrapianto nel prossimo futuro: riservato al rischio standard?
Quale ruolo per DaraRD (paziente anziano e fragile)?

MM Ricaduto:
Quali sono i pazienti che riceveranno Cilta cell in 2 linea e quali la terapia standard (IsaKD e DaraPD)?
Quali i pazienti che riceveranno le combinazioni di Belantamab vs Bs vs CAR-T?
Come scegliere tra terapie mirate a GPRC5D vs BCMA?

Grazie per l'attenzione!

Save the data:

16° MEETING TRIVENETO SUL MIELOMA E GAMMOPATIE MONOCLONALI

Padova 20 Dicembre 2024 – Hotel Galileo